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Review Article

Use of urinary markers in cancer setting: A literature review

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ABSTRACT

Introduction: In bone metastases, the disruption of normal bone processes results in increased resorption and formation rates, which can often be quantitatively measured by biomarkers in the urine and blood. The purpose of this review is to summarize relevant studies of urinary markers used as a diagnostic and/or prognostic tool, as well as its potential and advances in directing therapy.

Methods: A literature search was conducted using Ovid MEDLINE (1950 to July 2014), EMBASE (1950 to 2014 week 30) and Cochrane Central Register of Controlled Trials (3rd Quarter 2014) to identify studies that detailed the use of urinary markers in the cancer setting, specifically involving markers for bone metastases. Search terms included “urinary markers”, “cancer”, and “bone metastases”.

Results: A total of 35 articles, with 24 original studies, were identified. In general, urinary markers can be used to detect early signs of bone metastases prior to skeletal imaging, but still must be used in conjunction with imaging to avoid false positive results. The use of urinary markers, such as N-telopeptide, as a prognostic tool remains controversial, but can provide information on the relative risk of skeletal related events (SREs), disease progression, as well as death. Finally, while urinary markers have shown to be potentially useful in confirming the efficacy of bone metastases treatments, exploring the appropriate dosages for treatment, and directing therapy, it is still unclear to what extent urinary markers should be reduced by.

Conclusion: The potential use of urinary markers in the management of bone metastases is promising as it can allow for earlier and more convenient detection of bone metastases in comparison to other techniques. However, additional studies involving prospective clinical trials are suggested to further examine the potential of urinary markers in developing appropriate treatment strategies and endpoints, especially in developing a clearer protocol on the extent urinary markers should be reduced by to correlate with achievement of clinical benefit.

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1. Introduction

Bone metastases are a common complication in advanced cancer patients. The incidence of bone metastases at postmortem examination is 73% for patients with primary breast cancer and 68% for patients with primary prostate cancer [1]. In bone metastases, what typically is a tightly regulated process of bone resorption and formation, is disrupted by the interaction of tumor cells with osteoclasts and osteoblasts in the bone [2]. The disruption of normal bone processes by the disease usually results in increased resorption and formation

rates, which can often be quantitatively measured by biomarkers in the urine and blood of patients.

The focus of this review is on urinary markers. As the process of urination is a natural body process, obtaining urinary markers is certainly a very convenient procedure. Examples of urinary markers include: calcium, hydroxyproline, N-terminal cross-linked telopeptide of Type I collagen (NTX), and C-terminal cross-linked telopeptide of Type I collagen (CTX), pyridinoline crosslinks (PYD), and deoxypyridinoline crosslinks (DPD).

Despite the convenience of urinary markers, their capabilities should not be underestimated. Urinary markers are still in need of further validation to enter routine clinical practice; however they are becoming increasingly important in the management of bone metastases. Changes in bone are often too slow for detection by imaging; therefore urinary markers can provide an alternative

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method to evaluate changes in disease status, even before such changes become clinically evident. Thus, urinary markers could potentially serve as a convenient and important diagnostic tool [3].

Many studies over the past 20 years have shown the potential of urinary markers in the detection of the presence of bone metastases [3–11], the use of urinary markers for its prognostic value in bone disease [2,4,12–20], as well as directing therapy for bone metastases patients [2,6,12–18,21–25]. The purpose of this review is to summarize relevant studies reporting the potential and advances in using urinary markers in the management of bone metastases.

2. Methods

A literature search was conducted using Ovid MEDLINE (1950 to July 2014), EMBASE (1950 to 2014 week 30) and Cochrane Central Register of Controlled Trials (3rd Quarter 2014) to identify studies that detailed the use of urinary markers in the cancer setting, specifically involving markers for bone metastases. Search terms included “urinary markers,” “cancer,” and “bone metastases.” Articles written in languages other than English were omitted from consideration.

3. Results

We identified a total of 34 articles, with 23 original studies, that detailed the use of urinary markers as a diagnostic tool, prognostic tool, or in directing therapy for patients with bone metastases. The results of the 23 original studies are summarized in Table 1. The criterion for inclusion was strictly for studies that examined urinary markers; as such, there are many more studies in the literature not included that examines other bone markers exclusively. Studies that included both urinary markers and other bone markers were not omitted.

3.1. Diagnostic use of urinary markers

The diagnostic potential of urinary markers in bone metastases is documented by seven studies in our search, indicating a relationship between increasing levels of urinary markers and the presence of metastatic bone disease [3–11]. Most commonly, the increase of urinary pyridinoline (PYD) and deoxypyridinoline (DPD) were seen as a possible indicator for bone metastases [4–7,10,11].

In a study by Ikeda et al., patients with new or recurrent prostate cancer with bone metastases were determined to have a higher urinary excretion of urinary pyridinoline (PYD) and deoxypyridinoline (DPD) than patients with benign prostatic hyperplasia (BPH), or with prostate cancer and no bone metastases [5]. The authors concluded that PYD and DPD appeared to be a useful marker for evaluating the activity of bone metastases [5].

Another study by Vinholes et al. confirmed the specificity of PYP and DPD as bone resorption markers in patients with bone metastases [6]. The study found that pyridinoline and deoxypyridinoline levels were increased in 70% of bone metastases patients when compared to healthy reference controls, while urinary calcium, previously thought to be a suitable indicator of bone metastases in early studies [26,27], was increased in only 40% of patients [6].

Cross-linked C-telopeptide collagen (CTX) and cross-linked N-telopeptide collagen (NTX) have also been used as urinary markers with the potential of identifying the presence of bone metastases [8,9,12,14–16,18]. In the study by Garner et al., 39 patients with prostate cancer and bone metastases had CTX levels

greater than 149% of healthy control levels [15]. Moreover, there was no increase in urinary markers for prostate cancer patients without bone metastases, further highlighting the possibility of CTX as a bone metastases identifier [15]. Many studies in which urinary NTX levels were used as a marker for bone metastases have been reported [14,15,25]. In fact, in a study by Demers et al., NTX measurement had the most significant association with the probability of bone metastases of all other urinary markers, with urinary DPD the second most predictive marker [4]. The significance of NTX levels over other markers was also determined in a study by Lipton et al. [22].

However, while urinary markers show much promise in being diagnostic tools for patients with bone metastases, urinary markers are currently not absolutely necessary nor sufficient for the diagnoses of the disease. Urinary markers can detect early signs of bone metastases before skeletal imaging, but imaging is still necessary to diagnose bone metastases with certainty. Elevated urinary markers may be present even in those without malignant diseases, which explain why they are always used in conjunction with imaging to avoid false positive results.

3.2. Prognostic use of urinary markers

The use of urinary markers as a prognostic tool has also been explored in many studies in the literature [2,4,12–20]. While other bone markers such as serum bone alkaline phosphatase (BAP) [2], serum BSP [28], serum PINP [29], and serum ICTP [30] have proved useful in the prognostic setting, NTX has been shown to be the most consistent urinary marker for prognostic use [2,30,31].

For example, Brown et al. monitored 238 patients with bone metastases secondary to prostate cancer, non-small cell lung cancer (NSCLC), and other solid tumors. Patients with high urinary NTX levels had an increased relative risk (RR) of SREs, disease progression, and death compared with patients with low NTX levels. The authors concluded that baseline NTX levels were most predictive of negative clinical outcomes [12].

An exploratory cohort analysis by Coleman et al. also found similar predictive potential in NTX [2]. Urinary measurements of NTX and serum bone alkaline phosphatase (BAP) were obtained from 1824 bisphosphonate-treated patients. Patients were grouped into categories of low (< 50 nmol/mmolcreatinine), moderate (50–99 nmol/mmolcreatinine), or high (> 100 nmol/mmolcreatinine) NTX levels. Risk of skeletal complications and disease progression increased by 2-fold in patients with high and moderate NTX levels compared with patients with low NTX levels. Compared with patients with low NTX levels, risk of death on study increased 4- to 6-fold with high NTX levels, and 2- to 4-fold in patients with moderate levels [2].

Despite many studies supporting the prognostic capability of urinary markers, there have been a few studies that have not confirmed these findings [19,20]. Specifically, Petriolo et al. found that bone markers were not prognostic of survival in patients with hormone-resistant prostate cancer and bone metastases treated with chemotherapy [19], while Seibel et al. concluded in their study that bone markers could not predict bone metastases in breast cancer patients [20]. Siebel later explained that the contradiction of conventional results were possibly due to the long-term variability of markers of bone turnover in patients with breast cancer [32]. In addition to the risk of attaining false positive results [33], the variability of markers is another limitation that has prevented urinary markers from being routinely used in clinical practice for prognostic value. It also reveals the inconsistency in results that may arise from similar studies with different patient cohorts. This heterogeneity should be more clearly distinguished between studies, and future research should focus on developing endpoints that are specific to certain patient cohorts. Nevertheless,

Table 1
Summary of results from original studies.

Author	Study type	Population	Treatment	Markers examined	Urinary marker use
Coleman et al. [2]	Retrospective review of three randomized phase III trials	1824 bone metastases patients with various primary cancer sites	1462 patients with zoledronic acid, 362 with pamidronate	Urinary markers: NTX; Other bone markers: BAP	Prognostic use and directing therapy; high NTX levels correlated with increased risk of skeletal complications, disease progression and death.
Percherstorfer et al. [3]	Prospective study	52 lung cancer patients, 27 patients with bone metastases, 25 without bone metastases	No treatment	Urinary markers: DPD; Other bone markers: serum Ca, ALP, BALP, and osteocalcin	Diagnostic use: all markers were higher in patients with bone metastases than those without bone metastases, with DPD and BALP being significantly higher.
Demers et al. [4]	Retrospective review	A total of 94 patients with newly diagnosed or progressive malignancy; 30 patients had metastases to the bone, 50 patients had metastatic cancer without overt bone involvement, 13 patients had local disease without bone metastases	No treatment	Urinary markers: PYD, DPD, and NTX; Other bone markers: BAP and ICTP	Diagnostic use; NTX had the most significant association with the probability of bone metastases.
Ikeda et al. [5]	Retrospective review	15 patients with benign prostatic hypertrophy (BPH), 17 patients with carcinoma confined to prostate, 26 patients with prostate cancer and bone metastases	No treatment	Urinary markers: PYD and DPD; Other bone markers: alkaline phosphatase (ALP)	Diagnostic use; patients with prostate cancer and bone metastases had higher PYD and DPD excretion than did patients with BPH, or carcinoma confined to prostate cancer
Vinholes et al. [6]	Retrospective review	20 patients with bone metastases and received at least one infusion of pamidronate 120 mg	Pamidronate	Urinary markers: Calcium, PYD, and DPD; Other bone markers: ALP and hydroxyproline	Diagnostic use and directing therapy; PYD and DPD appears to be useful marker in evaluating activity of bone metastases and their response to hormonal treatment in prostate cancer.
Aksoy et al. [7]	Retrospective review	20 patients with BPH, 23 patients with localized prostate cancer, and 11 patients with prostate cancer and bone metastases	No treatment	Urinary markers: DPD; Other bone markers: bone isoenzyme of alkaline phosphatase (BALP) and TALP	Diagnostic use: increase in DPD, BALP, and TALP levels correlated with the presence of bone metastases
Piedra et al. [8]	Retrospective review	21 patients with BPH, 31 patients with prostate carcinoma without bone metastases, and 15 patients with bone metastases exclusively	No treatment	Urinary markers: NTX, a-CTX, b-CTX, PINP, and ICTP; Other bone markers: BAP	Diagnostic use: these results support the use of PINP or b-CTX as a tool to confirm the presence or the absence of bone metastases in the first staging of prostatic carcinoma patients.
Dane et al. [10]	Retrospective review	22 patients with lung cancer and bone metastases, 38 patients with early stage lung cancer exclusively	No treatment	Urinary markers: DPD and PYD; Other bone markers: serum osteocalcin, calcium and total alkaline phosphatase (T-ALP)	Diagnostic use: high urinary D-PYD level may be an early sign of occult metastases in patients with no bone metastasis assessed by scintigraphic techniques.
Paterson et al. [11]	Prospective pilot study	20 patients with breast cancer, 10 with known bone metastases, 10 with no recognized metastases in bone	No treatment	Urinary markers: PYD and DPD	Diagnostic use: 8 of 10 patients with metastases had crosslink excretion values higher than reference level indicating that urinary collagen crosslink assays may have use in the early detection of metastatic spread to bone.
Brown et al. [13]	Retrospective review of two phase III trials of zoledronic acid; exploratory cohort study	441 patients with bone metastases in total; 203 with prostate cancer, 115 with NSCLC, and 123 with other solid tumors	Zoledronic acid	Urinary markers: NTX; Other bone markers: BAP	Prognostic use and directing therapy: baseline and recent bone marker levels, especially NTX were predictive of negative clinical outcomes in patients with bone metastases secondary to prostate cancer and to NSCLC and other solid tumors.
Martinetti et al. [14]	Prospective cohort study	42 patients with bone metastases and various primary cancer sites	Pamidronate	Bone markers: osteocalcin, bone alkaline phosphatase (BAP), PINP, ICTP, and NTX, D-PYR OPG and OPN	Prognostic use and directing therapy: biochemical markers of bone turnover, in particular ICTP and osteoprotegerin seem promising for predicting and objectively assessing the analgesic response to pamidronate treatment.
Zafeirakis et al. [15]	Prospective cohort study	36 patients with prostate cancer also suffering from bone metastases, treated with ¹⁸⁶ Re-HEDP.	¹⁸⁶ Re-HEDP	Bone markers: osteocalcin, BAP, PINP, PICP, NTX, and CTX	Prognostic use and directing therapy: the best marker-derived predictors of better and longer duration of response to ¹⁸⁶ Re-HEDP treatment were a post-

Table 1 (continued)

Author	Study type	Population	Treatment	Markers examined	Urinary marker use
Garnero et al. [16]	Prospective cohort study	39 patients with prostate cancer and bone metastases, 9 patients with prostate cancer without bone metastases, 9 patients with BPH, and 355 healthy men	Pamidronate	Urinary markers: CTX; Other bone markers: serum osteocalcin, T-ALP, BAP, and PICP	treatment decrease in NTX of $\geq 20\%$ and a pretreatment NTX/PINP ratio of ≥ 1.2 . Prognostic use and directing therapy: 39 patients with prostate cancer and bone metastases had CTX levels greater than 149% of healthy control levels. In addition, pamidronate significantly decreases CTX levels by greater than 60%.
Berruti et al. [17]	Prospective study	35 prostate cancer patients with bone metastases	Pamidronate	Urinary markers: Ca, PYD, DPD, and NTX; Other bone markers: Ca, TALP, BGP, and ICTP; Other markers: Interleukin 6 (IL-6)	Prognostic use and directing therapy: pamidronate is able to induce a decrease in bone resorption, with NTX being the most sensitive marker in bisphosphonate therapy monitoring; however, changes in (IL-6), and not bone resorption markers maybe useful in prediction of symptomatic response.
Chow et al. [18]	Prospective cohort study	135 patients with bone metastases	Palliative radiotherapy	Urinary markers: Ca, creatinine, magnesium, phosphate, NTX, and PYD	Prognostic use and directing therapy: baseline levels of urinary markers could not predict which patient would benefit from palliative radiotherapy
Costa et al. [19]	Prospective study	97 patients with bone metastases (52 of which also had extraskeletal metastases) and 26 with extrasosseous disease only	49 patients received pamidronate, 3 received clodronate	Urinary markers: NTX; Other bone markers: BAP and ICTP	Prognostic use and directing therapy: with disease progression in bone, percent change from mean levels during stable disease was 152% for NTX and 144% for ICTP, regardless of the type of bisphosphonate therapy. NTX also had the highest positive predictive value (71%) for the diagnosis of bone metastases progression.
Petrioli et al. [20]	Prospective cohort study	141 patients with hormone-resistant prostate cancer and bone metastases	chemotherapy	Urinary markers: Calcium/creatinine ratio; Other bone markers: BALP, PICP, and ICTP	Prognostic use: bone markers were not prognostic of survival in patients with hormone-resistant prostate cancer and bone metastases treated with chemotherapy
Seibel et al. [21]	Prospective cohort study	113 patients with bone metastases and primary breast cancer	No treatment	Urinary markers: PYD, DPD, NTX, and CTX; Other serum bone markers: TAP, BAP OC, PICP, NTX, and CTX	Prognostic use: 93% of all changes in bone markers were below the least significant change, as defined in an independent group of similar patients. The remaining 7% of values could not be associated in a consistent pattern with the occurrence of BM. Authors conclude that in patients with primary breast cancer, bone markers cannot be used to predict or diagnose incident BM.
Brown et al. [22]	Prospective randomized trial	125 patients with bone metastases	Clodronate	Urinary markers: NTX and calcium; Other bone markers: Serum CTX	Directing therapy: the study found that doses of > 1600 mg clodronate produced mean reductions of $> 40\%$ in all three markers. The study confirmed the efficacy of the 1600 mg dose as the most appropriate dose for patients with primary breast cancer, but suboptimal for other (mainly prostate cancer) patients, who showed more optimal responses to 2400 mg.
Lipton et al. [23]	Prospective randomized cohort study	52 postmenopausal breast cancer patients with bone metastases	Pamidronate or placebo with standard endocrine therapy or chemotherapy	Urinary markers: PYD, DPD, and NTX	Directing therapy: Measuring NTX levels appears useful in monitoring bisphosphonate therapy of bone metastases, with the goal being to normalize NTX levels.
Vinholes et al. [24]		52 patients with painful bone metastases		Urinary markers: Ca and Hyp; Other collagen	Directing therapy: Symptomatic response during the first four

Table 1 (continued)

Author	Study type	Population	Treatment	Markers examined	Urinary marker use
	Prospective randomized double-blind trial		Two-hour infusion of pamidronate 120 mg or identical infusion of saline	breakdown products: NTX and DPD	weeks was seen after pamidronate, but not with placebo. Benefit of intravenous pamidronate is confirmed, with NTX levels decreasing by 70% after treatment.
Jagdev et al. [25]	Prospective randomized trial	51 patients with bone metastases	Oral clodronate 1600 mg daily, intravenous clodronate followed by same schedule of oral clodronate, intravenous pamidronate 90 mg monthly	Urinary markers: CTX and NTX	Directing therapy: intravenous pamidronate appears to be more effective than oral clodronate in both controlling symptoms and suppressing bone resorption.
Hoskin et al. [26]	Prospective cohort study	22 patients with bone metastases and various primary cancer sites	Radiotherapy	Urinary pyridinium and PICP	Directing therapy: an association was shown between relief of metastatic skeletal pain by radiotherapy and low marker concentrations before and after treatment, lending support to the hypothesis that relief of metastatic bone pain by radiotherapy relates to an effect on bone, rather than tumour physiology.

urinary markers are useful in that they can help identify patients who are at high risk of SREs, and allow for early therapeutic interventions.

3.3. Directing and monitoring therapy

Bisphosphonates have long been used in the treatment of patients with bone metastases [34]. Its ability to reduce morbidity and alleviate pain in skeletal metastases is undisputed. However, there is still a need to develop methods that can determine therapeutic efficacy and monitor patient response. Urinary markers have a rapid response to bisphosphonate treatment, and have proven to be a convenient and useful tool in validating the efficacy of bone metastases treatments, exploring the appropriate dosage required for treatment, and potentially helping to direct therapy. Many studies have explored the use of urinary markers in directing and monitoring treatment [2,6,12–18,21–25].

A study by Garnero et al. examined the effect of pamidronate treatment on urinary markers in patients with bone metastases and prostate cancer. It was found that after bisphosphonate treatment, the urinary a-CTX, urinary b-CTX and serum CTX, decreased significantly by an average of 65%, 71%, and 61% respectively within a few days. These findings, coupled by the result that no significant change was observed for any bone formation markers, suggest that CTX may be useful for management of this group of patients [15]. More importantly, the effect of bisphosphonates in bone metastases is measured quantitatively.

In addition, urinary markers have also been used to confirm the efficacy of appropriate dosages for treatment. For example, Brown et al. explored the dose-response relationship of clodronate with markers urinary NTX, serum CTX, urinary calcium, and BAP, measured weekly for a 6-week treatment period. 125 patients with bone metastases were randomized to daily oral clodronate (800, 1600, 2400, and 3200 mg). The study found that doses of > 1600 mg clodronate produced mean reductions of > 40% in all three markers. The study confirmed the efficacy of the 1600 mg dose as the most appropriate dose for patients with primary breast cancer, but suboptimal for other (mainly prostate cancer) patients, who showed more optimal responses to 2400 mg [21].

Finally, a study by Zafeirakis et al. highlighted the use of urinary markers in directing treatment. In this prospective study, bone markers such as PINP, PICP, NTX and CTX were compared with the

level and duration of pain response to radionuclide treatment in 36 men with prostate cancer suffering from osseous metastases. According to multivariate and ROC analyses, the best marker-derived predictors of better and longer duration of response to ^{186}Re -HEDP treatment were a post-treatment decrease in NTX of $\geq 20\%$ and a pretreatment NTX/PINP ratio of ≥ 1.2 . This study shows the usefulness of urinary markers in providing cut-off values for a cohort of patients that do not respond to a certain palliative treatment, thereby helping patients to avoid inefficient and expensive treatment [14].

Despite promising results showing the use of urinary markers in directing therapy, the exact amount that urinary markers should be reduced by as indication of treatment success remains unknown [35]. Although some studies have shown that only patients with normalized urinary markers following bisphosphonate treatment experience a significant improvement in pain and related symptoms [23,24], whether to normalize NTX, reduce NTX by an absolute or a proportional amount, or merely stabilize baseline levels as a way of aiming at optimally improved patient outcomes is still unclear and requires additional long term studies [35].

4. Conclusion

The use of urinary markers in diagnosing, prognosticating, and directing therapy for bone metastases patients is well documented in the literature. In general, the urinary markers can detect early signs of bone metastases before skeletal imaging, but are still only used in conjunction with more established imaging techniques to avoid false positive results. The use of urinary markers as a prognostic tool, though not completely conclusive, especially in primary breast cancer patient cohorts, can provide information on the RR of SREs, disease progression, as well as death. Finally, while urinary markers have shown to be potentially useful in directing therapy, it is still unclear to what extent urinary markers should be reduced by. Further studies involving prospective clinical trials are suggested to further examine the potential of urinary markers in developing appropriate treatment strategies and endpoints, especially in developing a clearer protocol on the extent urinary markers should be reduced by to correlate with achievement of clinical benefit. Until then, urinary markers should not be used in isolation in routine clinical settings.

Conflicts of interest

None.

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